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Title: Prognostic Tools in Patients with Advanced Cancer: A Systematic Review

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Abstract

PURPOSE

In 2005, the European Association for Palliative Care (EAPC) made recommendations for prognostic markers in advanced cancer. Since then, prognostic tools have been developed, evolved and validated. The aim of this systematic review was to examine the progress in the development and validation of prognostic tools.

METHODS

Medline, Embase Classic + and Embase were searched. Eligible studies met the following criteria: patients with incurable cancer; >18 years; original studies; population n≥100; published after 2003. Descriptive and quantitative statistical analyses were performed.

RESULTS

Forty-nine studies were eligible, assessing seven prognostic tools across different care settings, primary cancer types and statistically assessed survival prediction. The (PPS) Palliative Performance Scale was the most studied (n=21,082), composed of 6 parameters (6 subjective), was externally validated and predicted survival. The Palliative Prognostic Score (PaP) composed of 6 parameters (4 subjective, 2 objective), the Palliative Prognostic Index (PPI) composed of 9 parameters (9 subjective), and the Glasgow Prognostic Score (GPS) composed of 2 parameters (2 objective), and were all externally validated in more than 2000 patients with advanced cancer and predicted survival.

CONCLUSION

Various prognostic tools have been validated, but vary in their complexity, subjectivity and therefore clinical utility. The GPS would seem the most favourable as it uses only two parameters (both objective) and has prognostic value complementary to the gold standard measure, which is performance status. Further studies comparing all proven prognostic

markers in a single cohort of patients with advanced cancer, are needed to determine the optimal prognostic tool.

Key words: prognostic tools, cancer, review

Running title: review of prognostic tools in advanced cancer

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Introduction

Estimating prognosis is a fundamental component in the management of patients with advanced cancer for several reasons. Firstly, accurate estimation of prognosis can help inform whether anti-cancer treatment is likely to be beneficial.[1,2] Secondly, it may relieve patient and carer anxiety associated with prognostic uncertainty.[3] Thirdly it can help with end of life care planning, including place of care.

However, in patients with advanced cancer the ceiling limit of the TNM classification system is often reached (i.e. M_1) and as such is of limited value. As such, in the clinic, prognosis is based on various factors including stage of disease, performance status, previous clinical experience and knowledge of cancer trajectories. However the subjective nature of these may result in estimates of prognosis which are inaccurate, potentially misleading and may result in anti-cancer therapies being given inappropriately.[2,4-6]

In an attempt to improve prognostic accuracy, in 2005the European Association of Palliative Care (EAPC) published recommendations on the use of prognostic markers in patients with advanced cancer.[7] These recommendations were informed by eight studies examining different prognostic tools, which had been published in the preceding decade (1993-2003), and recommended a number of prognostic tools and their utilisation. These tools were: the Terminal Cancer Prognostic Score, the Palliative Performance Scale, the Palliative Prognostic Index and the Palliative Prognostic Score.

Since these recommendations were made, a plethora of prognostic tools devised for use in patients with advanced cancer have been developed, however to date they have not been presented together and comparison made. To this end, the aim of this systematic review, was

to examine and compare prognostic tools in patients with advanced cancer and make recommendations for their use.

Methods

The following databases were searched: Medline (2003– 2015), Embase Classic + and Embase (2003 -2015). The search focussed on studies of prognostic tools in patients with advanced cancer regardless of the original primary tumour. The search terms are listed in Appendix 1. A hand search of key journals and relevant citations was carried out. The date of the last literature search was 30th April 2015.

Eligibility Criteria

Eligible studies met the following inclusion criteria: population with advanced cancer (defined as an incurable cancer); original studies; study population n $\geq$100 and age $\geq$ 18 years; quantitative clinical and/or biomarkers were examined; a multivariate statistical model was described; the tool had been examined and validated in two or more independent data sets; published in English; published after 2003 (end date of original literature search); and full paper was available.[7] The primary outcome measurement examined was survival prediction (likelihood of death) based on the use of the prognostic tool in the specific patient population. Studies were excluded if: a univariate survival analysis was described only; the tool was designed for use in one specific population with one specific cancer type (e.g. only patients with specific stage of lung cancer) or qualitative indices were used exclusively to predict survival.

Data extraction and analysis

The initial database search was undertaken and duplicates removed. Two authors (CS and KM) independently screened each study for eligibility based on the abstract and finally each full text article. From this, the necessary data for descriptive and quantitative analyses were extracted by CS and TS, independently. These included the descriptors of the patient population, length of survival and information regarding survival predictions. The analysis of each study was performed using standard quality assessment criteria which were then summarised for statistical analysis and comparison where possible.[8] Studies are presented according to the prognostic tool described. Where studies examined both populations with cancer and non-cancer, only those populations with cancer were included in the analysis.

Results

The literature search process is shown in Figure 1. Following abstract review, 179 articles were reviewed in full and this resulted in 49 studies fulfilling the eligibility criteria.

From the 49 eligible studies, seven different prognostic tools were identified. A summary of these is detailed in Table 1. The tools identified were the PaP (Palliative Prognostic Score - 8 studies), D-PaP (Delirium-PaP - 2 studies), BCI (B12/CRP Index -1 study), PiPS (Prognosis in Palliative Care Study- 1 study), PPI (Palliative Prognostic Index -8 studies), PPS (Palliative Performance Scale - 18 studies) and the GPS (Glasgow Prognostic Score -10 studies).

A detailed description of these seven prognostic tools is given in Appendices 2 and 3. These tools used a combination of clinical and/or biomarker parameters. The most common clinical parameters used were performance status, anorexia and dyspnoea. The most common biomarkers were C-reactive protein (CRP), white cell count, lymphocyte count and albumin.

The number of parameters used ranged from two (GPS, BCI) to 17 (PiPS B), and the mean number was seven. The largest single population studied for each of the prognostic tools is summarised in Table 2. Details of all studies included in this review are summarised in Supplementary Table 1.

To date, there have been eight studies (combined total n=2694) examining the PaP in patients with advanced cancer. Patient cohorts were unselected but included patients with a variety of cancer diagnoses including cancer of the head and neck, lung, skin, breast, gastrointestinal tract, genitourinary tract, prostate, gynaecological, neuroendocrine and haematological tissue. The studies were from groups in Australia (1 study), Italy (2 studies), Brazil (1 study), Japan (1 study), Canada (2 studies) and the USA (1 study), thereby providing external validation of the tool. Two studies, (n=910) examined the D-Pap in patients with advanced cancer.[9,10] This included patients with cancers of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract. Both the PaP and D-PaP predict survival in patients with advanced cancer. The D-PaP tool has not been as extensively validated compared with the PaP, however both perform similarly when compared with each other. [9]

To date, one study comprising 329 patients examined the BCI in patients with advanced cancer.[11] The patient population included those with a diagnosis of cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynaecological, neuroendocrine and haematological tissue. This study confirmed that an elevated BCI predicts poor survival.

One study (n=1018) has examined the PiPS.[12] The patients included those with diagnoses of gastrointestinal, lung, unknown primary, breast, urological, gynaecological, central nervous

system, haematological and head and neck cancers. This study reported that the area under the curve (AUC) varied between 0.79 (PiPS A) and 0.86 (PiPS B), and suggested that PiPS is at least equal to and may be better than the clinician's predicted survival.

Eight studies (n= 5929) have examined the prognostic value of the PPI.[9,13-20] The patients included those with cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynaecological and haematological tissue. The studies were based in Japan (3 studies), Italy (1 study), Taiwan (2 studies), USA (1 study) and Canada (1 study). Recently studies have examined a change in PPI scores, and this approach to researching the PPI appears more consistent, accurate and clinically useful.

Eighteen studies (n=21,082) have examined the PPS. The patients included those with diagnoses of cancer of the head and neck, lung, breast, gastrointestinal tract, genitourinary tract, prostate, gynaecological, neuroendocrine and haematological tissue. The studies were based in the USA (6 studies), Spain (1 study), Canada (8 studies), Italy (1 study), Singapore (1 study) and South Korea (1 study), thereby providing external validation of the tool. Due to the numerous subgroups within the tool, earlier reports had stated it was not highly discriminating in the intermediate scores.[7] Studies taking place after 2005 tackled this issue and focussed on the significance of a 10% decrement in PPS score or poorer PPS scores. A strong ordering effect across the different PPS categories was demonstrated, with highly accurate scores for a PPS of 40% or less. Patients with PPS categories greater than 50% had lower hazard ratios than patients with lower PPS scores.

Ten studies (n=5163) have examined the GPS. The patients included those with diagnoses of cancer of the head and neck, lung, skin, breast, gastrointestinal tract, genitourinary tract,

prostate, gynaecological, neuroendocrine and haematological tissue. Eight studies were from groups based in the UK, one study was from Japan and one study examined data from an international bio bank of patients, providing external validation of this tool.

A descriptive comparison of the individual clinical and biomarkers parameters included in the each of the prognostic tools is shown in Table 3. The number of markers ranges from 2 (GPS) to 17 (PiPSB). The (PPS) is composed of 6 parameters (6 subjective), the Palliative Prognostic Score (PaP) composed of 6 parameters (4 subjective, 2 objective) the Palliative Prognostic Index (PPI) composed of 9 parameters (9 subjective), and the Glasgow Prognostic Score (GPS) composed of 2 parameters (2 objective).

To date, there have been limited studies on the direct comparison of the prognostic value of the above tools. One study compared the performance of the PaP to the D-PaP, PPS, and PPI and concluded that the PaP showed superior accuracy and reproducibility.[9] The PaP was also directly compared with the PPS and PPI tools in separate studies.[20,21] Tarumi et al. concluded that the PPS and the PaP performed similarly in survival prediction,[21] whereas Kim et al. concluded that the PaP performed better.[20]

Finally, direct comparison has been carried out between the GPS and ECOG performance status,[22] and between the GPS and the PPI[23] and reported that the GPS had prognostic value independent of ECOG-PS[22] and PPI[22,23].

Discussion

Since the European Association for Palliative Care recommendations for prognostic tools were published in 2005 there have been a number of prognostic tools developed, evolved, and validated.[7] The PPS has been studied in the greatest number of patients, externally validated and consistently predicts survival in patients with advanced cancer. Other prognostic tools of note, that have been validated and consistently predict survival are the PaP, the PPI, and the GPS. In addition, the latter (based on the combination of C-reactive protein and albumin), has been extensively validated since the original review.

Most of the prognostic tools (PPS, PaP and the PPI) depend largely on the assessment of functional status as a core component. Therefore, their use in routine practice has been sparse compared to Karnofsky Performance Score or the simplified Eastern Cooperative Oncology Group Performance Score.[24,25] In addition the relatively complex scoring systems of these prognostic tools may have prejudiced their routine use; whilst the similarities but clear differences in these is confusing and makes comparison challenging. Therefore, it would be important to rationalise these subjective assessments into a simpler scheme with as advocated by Harding and co-workers.[26]

From the present review it is also clear that many of the tools such as PaP, PPI, PPS and even performance status are predominantly subjective and it could be argued that where possible, these should be made more objective. For example, one such way would be to examine if skeletal muscle mass is related to functional status, and whether it can be a surrogate marker of physical function. This would seem plausible as skeletal muscle indices are increasingly recognised to have prognostic value.[27]

Although various prognostic tools have been validated they vary in their complexity,

subjectivity and therefore their clinical utility. The GPS would seem the most favourable as it uses only two parameters (both objective) and has prognostic value complementary to ECOG performance status, most commonly used assessment of patient physical function, in the oncology of advanced disease. Further studies comparing all externally validated prognostic tools in a single cohort of patients with advanced cancer, are needed to determine the optimal prognostic tools.

The search strategy in the present review was comprehensive and included the main medical databases and a detailed search strategy (appendix 1). However, there were three notable studies not included in the review. Feliu and coworkers reported the development and validation of a prognostic nomogram for terminally ill patients with cancer in almost 900 patients.[28] However, it is of interest that the nomogram included the components ECOG-ps, LDH, lymphocyte count and albumin concentrations that have been used in other externally validated prognostic scores such as PaP that have been examined in the present review. The second study by Kim and coworkers reported the external validation of PiPS-A and PiPS-B in 202 terminally ill patients with cancer.[29] Finally, our search was limited to 30th April 2015. This excluded a large external validation study (n = 2,426) of the modified PiPS-A and -B prognostic tools reported by Baba and coworkers in May 2015.[30] Nevertheless present review is therefore a step towards the viewpoint of Harding and coworkers that '*it would be important to rationalise these subjective assessments into a simpler scheme with "judicious selection and refinement of existing tools'* (The PRISMA Symposium 1: outcome tool use. Disharmony in European outcomes research for palliative and advanced disease care: too many tools in practice).[31]

Limitations

It is clear that with the exception of the GPS and contrary to the REMARK guidelines, HR and 95% CI have been reported inconsistently in the prognostic tools developed for use in patients with advanced cancer. This precluded meaningful meta-analysis in the present systematic review. Therefore, future research should directly compare these validated prognostic tools within all advanced cancer types using similar statistical approaches, in keeping with the REMARK guidelines.[32]

The present systematic review updated a previous review published a decade ago. The majority of the prognostic tools examined had less than five independent reports of their prognostic value and therefore a meta-analysis of the validated prognostic tools was not meaningful and a formal estimate of bias was not carried out. However, the data from each paper was presented in detail (supplementary Table 1) enabling the reader to draw conclusions as to their quality and the likelihood of bias using standard criteria. As a result the present systematic review is largely descriptive giving an update in the progress of prognostic tools in the field.

Several key aspects of prognostic tools remain elusive and the present manuscript was unable to address these due to paucity of primary data. To illustrate, it is not clear if certain tools have greater utility in specific tumour types and/or at certain points in the cancer journey. Further, the potential role of these clinical tools in clinical practice is unclear as their usefulness in treatment stratification or place of care planning is unknown; both of these are unlikely to be addressed unless such tools are incorporated into routine clinical practice.

It is also clear that another challenge is to implement the right tool at the right point in the patient's cancer journey. This is important as this can affect different aspects of care e.g. whether to treat with anti-cancer therapy, preferred place of death etc. To date the application of the right tool, at the right time remains elusive and is likely to require a combination of mixed methodologies to achieve this.

Conclusion

Prognosis remains a central tenet of care in cancer, and validated tools applied correctly may serve to improve patient care. Since the previous systematic review and recommendations, many prognostic tools that have been examined are not integrated into routine clinical care. It could be argued that the multitude of tools available may have actually confused clinicians as to the optimal tool for use. Further, as performance status remains at the forefront of clinical decision making regarding prognosis, tools which build on this would seem preferable e.g. the GPS and ECOG-PS. To provide some clarity as to the optimal prognostic tool, studies are needed which compare all independent prognostic markers, in a single population. Such studies are eagerly awaited.

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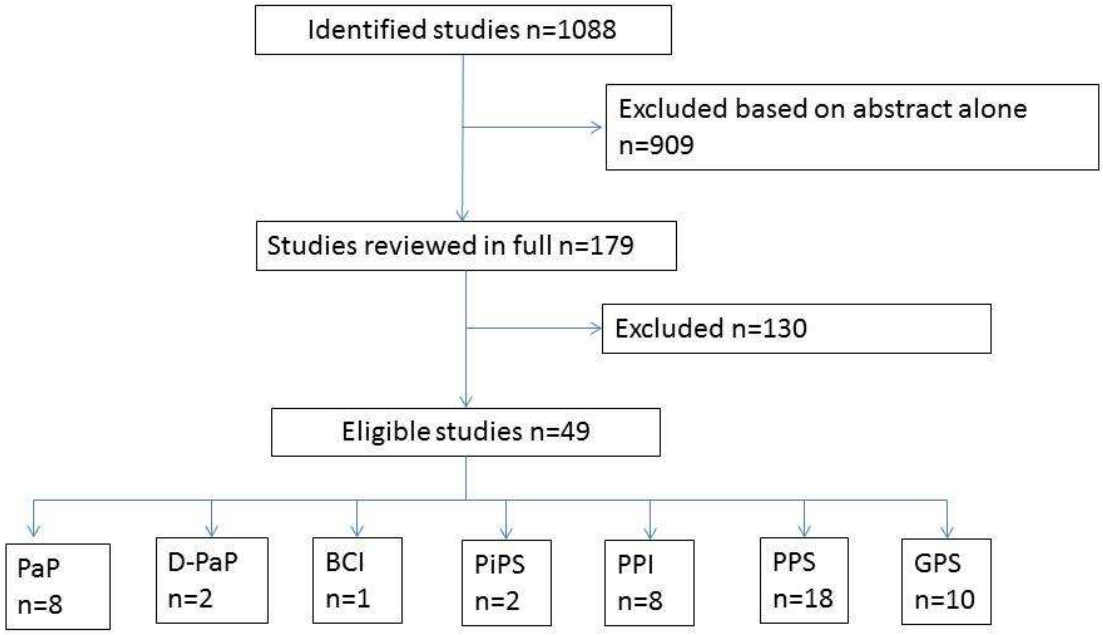

Figure 1. Flow chart of the review process

Table 1 - Summary of Prognostic Tools

Tool	Number of variables		Cancer types (mixed/single)	Number of studies***
	Clinical* (subjective)	Biomarkers** (objective)		
PaP	4	2	Mixed and single	8
D-PaP	5	2	Mixed only	2
BCI	0	2	Mixed only	1
PiPS A PiPS B	13 9	0 9	Mixed	1
PPI	5	0	Mixed only	8
PPS	7	0	Mixed only	18
GPS	0	2	Mixed and single	10

*Clinical refers to signs or symptoms which are of prognostic significance

**Biomarkers refers to serum biomarkers of prognostic significance

***studies eligible for inclusion

Table 2 – Summary of Prognostic Tools –Largest Population Studied per Tool.

Tool	Authors	Cancer	N	Survival Outcome	Survival*	HR**	Summary	P Value*
PaP	Tarumi et al[21]	Various	777	Continuous	35d	-	**Multivariate Cox regression model on overall survival:** Including age, gender, diagnosis, initial PPS, initial PaP, MMSE score, and presence/absence of delirium on initial consultation. **Log rank test:** PaP Group A vs. group B vs. group C	<0.001
D-PaP	Maltoni et al[9]	Various	549	Categorical (21d and 30d)	22d	-	AUC 0.73 (95%CI 0.71-0.74)	<0.0001
BCI	Kelly et al[11]	Various	329	Categorical (90d)	42d	-	**Log rank test:** BCI Group 1 vs. group 2 vs. group 3	< 0.001. (group 1vs. group 2 P = 0.091)
PiPS	Gwilliam et al[12]	Various	1018	Continuous	< 1 – 14w	-	AUC= 0.79-0.86	-
PPI	Kao et al [33]	Various	2392	Continuous	5w	0.63	**Multivariate Cox Regression:** Adjusting for age, gender, primary cancer origin, referring medical department, and the interval between the hospital admission and referral dates	< 0.001
PPS	Casarett et al[34]	Various	7391	Categorical (7d)	-	-	**Multiple logistic regression:** Probability of dying between PPS groups.	< 0.001
GPS	Laird et al[22]	Various	2456	Categorical (3m)	3.2m	1.51-2.27	**Multivariate Cox proportional hazards model on overall survival:** *Test sample:* Including age, cognitive function, dyspnea, appetite loss, quality of life, physical function, role function, fatigue, BMI, performance status and mGPS. HR 1.62–2.05 *Validation sample:* Including quality of life, physical function, emotional function, pain, BMI, performance status and mGPS. HR 1.51–2.27 **Log rank test:** Comparing levels of mGPS	< 0.001 < 0.01 < 0.001

Supplementary Table 1 – Prognostic Tools

Tool	Authors	Cancer	N	Survival Outcome	Survival*	Summary	HR**	P Value*
PaP	Glare et al[35]	Various	100	Categorical (4w)	12w	**Log rank (test for trend):** Probability of surviving 1 month: Group A vs. Group B vs. Group C	-	<0.0001
	Tassinari et al[36]	Various	173	Continuous	26w	**Multivariate Cox regression model on overall survival:** Including age, tumour type, number of metastatic sites, performance status, ESAS, PaP score.	-	0.022
	Naylor et al[37]	Various	250	Categorical (30d)	95d	**Log rank test:**PaP Group A vs. Group B vs. Group C	-	<0.0001
	Hyodo et al[38]	Various	208	Continuous	27d	**Cox proportional hazards:** PaP Group B vs. Group A PaP Group B vs. Group C	 0.536 (0.36-0.779) 3.72 (2.59-5.35)	 0.002 <0.001
	Tarumi et al[21]	Various	777	Continuous	35d	**Multivariate Cox regression model on overall survival:** Including age, gender, diagnosis, initial PPS, initial PaP, MMSE score, and presence/absence of delirium on initial consultation. **Log rank test:** PaP Group A vs. group B vs. group C	-	<0.001
	Maltoni et al[9]	Various	549	Categorical (21d and 30d)	22d	**Log rank test** PaP Group A vs. group B vs. group C	-	< 0.001
	Kim et al[20]	Various	415	Categorical (4w)	-	A score of >10 was the optimal cut-off for predicting survival at 4 weeks	-	-
	Hui et al[39]	Various	222	Continuous	106d	**Cox proportional hazards regression analysis with backward selection:** Incorporating age, sex, PaP, PPI, serum albumin, fat-free mass, unadjusted phase angle, handgrip strength, maximal inspiratory pressure, and standardized phase angle.PaP **Log rank test:**PPI group A vs. group B vs. group C	1.07(1.02-1-13)	0.008 < 0.001
D-PaP	Maltoni et al[9]	Various	549	Categorical (21d and 30d)	22d	D-PaP Group A versus Group B vs Group C	-	<0.001
	Scarpi at al[10]	Various	361	Categorical (30d)	4w	**"Validation by calibration" and K statistic**	1.6 (1.22-1.99)	<0.001
BCI	Kelly et al[11]	Various	329	Categorical (90d)	42d	**Log rank test:** BCI Group 1 vs. group 2 vs. group 3	-	< 0.001
PiPS	Gwilliam et al[12]	Various	1018	Continuous	< 1 – 14w	**Logistic Regression** AUC= 0.79-0.86	-	-
PPI	Stone et al[15]	Various	194	Continuous	Group1: 68d	**Cox proportional hazards:** The Hazard Ratio associated with a one unit increase in PPI score	1.36 (1.29-1.43)	< 0.001

					Group2: 21d Group3:5d	Survival of less than three weeks was predicted with a PPV of 86% and negative predictive value NPV of 76%.		
	Maltoni et al[9]	Various	549	Categorical (21d and 30d)	22d	PPI Group A versus Group B vs Group C	-	<0.001
	Cheng et al[18]	Various	623	Categorical (21d)	-	**Cox proportional hazards:** Group C vs. Group A: Group C vs. Group B:	 0.19 (0.10-0.24) 0.54 (0.43-0.69)	 <0.001 <0.001
	Kim et al[20]	Various	415	Categorical (4w)	-	Optimal scores for predicting 4wk survival over 4.5	-	-
	Arai et al[19]	Various	374	Categorical (3w)	-	**Multivariate Cox proportional hazards model on predicting death within 3 weeks:** Including gender, age, BMI, BT, SBP, diastolic blood pressure, PR, initial PPI, and Δ PPI.	9.0 (4.1-20.0) to 14.4 (5.7-36.2)	< 0.01
	Kao et al [33]	Various	2392	Continuous	5w	**Multivariate Cox Regression:** Adjusting for age, gender, primary cancer origin, referring medical department, and the interval between the hospital admission and referral dates	0.63	< 0.001
	Hui et al[39]	Various	222	Continuous	15w	**Log rank test:** PPI group A vs. group B vs. group C **Cox proportional hazards regression analysis with backward selection:** Incorporating age, sex, PaP, PPI, serum albumin, fat-free mass, unadjusted phase angle, handgrip strength, maximal inspiratory pressure, and standardized phase angle.	- -	0.03 -
	Miura et al[40]	Various	1160	Categorical (3w, 6w)	<8w	**Cox regression analysis:** Adjusted for primary cancer site, age, and gender. PPI=4-6 PPI≥6	 1.11 (0.89-1.38) 1.56 (1.27-1.92)	 0.376 <0.001
PPS	Head et al[41]	Various	261	Continuous	29d	**Cox Proportional Hazards model on overall survival:** Independent variables included PPS score category, comorbidity status, diagnosis, age, gender, race, and marital status.	0.18(0.092-0.34) to 0.43 (0.28-0.66)	<0.05
	Harrold et al[42]	Various	214	Categorical (7d, 30d, 90d, 180d)	-	**Univariate Cox proportional hazards modeling:** **The area under the receiver operating characteristic (ROC) curve:** To measure predictive accuracy in cancer pts. and non-cancer patients.	0.96	<0.001
	Sanchez et al[43]	Various	250	Continuous	32d	**Cox regression analysis on overall survival: PPS≤50** Adjusted for anorexia; compromised oral intake; agitation; delirium; apathetic mental state; confused or in coma; coherent language;	2.21 (1.30-3.76) to 8.33 (4.51-15.38)	< 0.05

						orientation in time, place, and person; hallucinations and/or illusions; heart rate; respiratory rate; PPS.		
	Lau et al[44]	Various	647	Continuous	10d	**Log rank test on overall survival:** PPS groups	-	< 0.001
	Olajide et al[45]	Various	157	Continuous	9d	**Proportional hazards regression model on overall survival:** Including PPS, dyspnea, pain, fatigue, and agitated delirium. 10% decrease in PPS results in HR of 1.65	1.65 (1.42-1.92)	< 0.001
	Lau et al[46]	Various	126	Continuous		Cox Regression	0.29 to -0.93	<0.001
	Lau et al[47]	Various	347	Continuous	37d	**Log rank test on overall survival:** Initial PPS groups Increasing HR with increasing PPS group **Multivariable Cox proportional hazards model on overall survival:** Including gender, diagnosis, site and PPS. Increasing HR with increasing PPS group (PPS20%[0.40] to PPS 70%[0.039])	- 0.039 (0.023-0.067) to 0.40 (0.25-0.64)	< 0.001 < 0.001 < 0.001
	Weng et al[48]	Various	492	Continuous	18d	**Log rank test on overall survival** PPS group A vs. group B vs. group C **Cox proportional hazards model on overall survival:** Including age, gender, race/ethnicity, and PPS.	- 0.96 (0.95-0.07)	< 0.05 < 0.001
	Younis et al[49]	Various	180	Continuous	35d	**Multivariate analysis with Cox proportional hazards model on overall survival:** Including executed advanced directives, Medicare/Medicaid insurance, PPS and gender.	1.73 (PPS<50)	< 0.05
	Lau et al[50]	Various	5097	Continuous	39d	**Log rank test on overall survival** PPS groups compared **Cox proportional hazards model on survival:** Including age, gender, location, diagnosis category, and initial PPS. Increasing HR with PPS group (PPS 70 [0.056] – PPS 20 [0.54]).	- 0.056 (0.046-0.069) to 0.54 (0.49-0.61)	< 0.001 <0.001 <0.001
	Selby et al[51]	Various	1622	Continuous	26.5d	**Multivariate logistic regression analysis on overall survival:** Including gender and PPS.		Group A and C: P < 0.0001 Group B: P = 0.19
	Tarumi et al[21]	Various	777	Continuous	43d	**Cox proportional hazards model on overall survival:** Including age, gender, diagnosis, initial PPS, and survival curve time in	0.021(0.099-0.46) to	<0.001

						days, initial PaP, MMSE score, and presence/ absence of delirium on initial consultation (PPS90% [0.21] PPS 40% [0.45])	0.45 (0.31-0.66)	<0.001
	Casarett et al[34]	Various	7391	Categorical (7d)	-	**Multiple logistic regression:** Probability of dying between PPS groups.	-	< 0.001
	Maltoni et al[9]	Various	549	Categorical (21d and 30d)	22d	**Log rank test:** PPS Group A vs. group B vs. group C	-	< 0.0001
	Mei et al[52]	Various	296	Categorical (90d)	-	**Multivariate Cox proportional hazards model on overall survival:** Including albumin, gender and baseline PPS scores (PPS 60-90%[0.31] PPS 20-30% [0.52])	0.31(0.16-0.58) to 0.52 (0.36-0.76)	<0.001 <0.001
	Kim et al[20]	Various	415	Categorical (4w)	-	Optimal scores for predicting survival ≤ 30	-	-
	Lee et al[53]	Various	606	Continuous	-	Change in score >30% significantly associated with survival	2.66 (2.19-3.22)	-
	Jang et al[54]	Various	1655	Continuous	133d	**Log-rank test for trend:** Median survival between groups.	-	< 0.001
GPS	Sharma et al[55]	Ovary	154	Continuous	39.9m	**Multivariate Cox proportional hazard model on cancer specific survival:** Including GPS, histological subtype, ascites, performance status, ALP, CRP and primary debulking surgery.	1.68 (1.16-2.45)	< 0.001
	Crumley et al[56]	Gastro-oesophageal	258	Continuous	-	**Multivariate Cox regression model on cancer specific survival:** Including tumour site, stage, alkaline phosphatase, the GPS and treatment.	1.51(1.22-1.86)	< 0.001
	Glen et al[57]	Pancreas	187	Categorical (12m)	4.6m	**Multivariate Cox regression analysis on overall survival:** Prognostic scores as covariates.	1.72 (1.40-2.11)	< 0.001
	Ramsey et al[58]	Renal	119	Continuous	8m	**Multivariate Cox proportional-hazards model on cancer specific survival:** Including lactate dehydrogenase, hemoglobin, calcium, white cell count, neutrophil count, albumin, and C-reactive protein.	2.35 (1.51-3.67)	< 0.001
	Forrest et al[59]	Lung	101	Continuous	Active treatment: 15.5m Palliative treatment: 5.8m	**Multivariate Cox regression analysis on overall survival:** Stratified for treatment	2.32(1.52-3.54)	< 0.001
	Partridge et al[60]	Various	296	Categorical (2w, 4w)	-	**Multivariable Cox regression model on overall survival:** Including sex, primary cancer site, age, hemoglobin, and white cell	2.71(1.25-5.88)	0.011

						count (mGPS 2=2.71)		
	Leung et al[61]	Lung	261	Continuous	8m	Multivariate analysis on cancer specific survival:	1.67 (1.28-2.19)	0.0001
	Pinato et al[62]	Lung	171	Continuous	9.7m	**Multivariate Cox proportional hazard model on overall survival:** Including gender, histologic subtype, PS, the European Organization for the Research and Treatment of Cancer Prognostic Score, WBC count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, CRP, albumin and mGPS.	2.6 (1.6-4.2)	<0.001
	Laird et al[22]	Various	2456	Categorical (3m)	3.2m	**Multivariate Cox proportional hazards model on overall survival:** *Test sample:* Including age, cognitive function, dyspnea, appetite loss, quality of life, physical function, role function, fatigue, BMI, performance status and mGPS. (mGPS 1[HR 1.62] mGPS 2 [2.05]) *Validation sample:* Including quality of life, physical function, emotional function, pain, BMI, performance status and mGPS. (mGPS1 [1.58] mGPS [2.06) **Log rank test:** Comparing levels of mGPS	 1.62 (1.35-1.93) to 2.05 (1.72-2.44) 1.58 (1.25-2.01) to 2.06 (1.62-2.63)	 <0.001 <0.001 <0.001 <0.001 < 0.001
	Miura et al[40]	Various	1160	Categorical (3w, 6w)	-	**Multivariate Cox regression analysis on overall survival:** Adjusted for primary cancer site, age, and gender. GPS=1 GPS=2	 1.07 (0.78-1.49) 1.36 (1.01-1.87)	 0.673 0.046

NB: Some studies compared several of these tools in one paper which explains the disparity in the total number of studies versus papers

*Median **Hazard Ratio (Confidence Interval). Where cells are blank, data was unavailable. d=days, w=weeks, m=months.

Table 3 – Clinical and bio-markers per prognostic tool.

		Prognostic Tool								
		PaP	D-Pap	BCI	PiPS-A	PiPS-B	PPI	PPS	mGPS	GPS
Clinical Marker	PS*	x	x		x	x	x	x		
	CPS**	x	x					x		
	Anorexia/decreased oral intake	x	x		x	x	x	x		
	Dyspnoea	x	x		x		x			
	Ambulation							x		
	Delirium		x				x	x		
	Activity							x		
	Evidence of disease							x		
	Oedema						x			
	Global Health				x	x				
	Breast Cancer				x					
	Male genital organs				x	x				
	Distant Metastases				x	x				
	Bone metastases				x	x				
	Liver metastases				x					
	Mental Test Score				x	x				
	Heart Rate				x	x				
	Dysphagia				x					
	Weight loss – last month				x					
	Fatigue					x				
Biomarkers	Lymphocyte count	x	x			x				
	White cell count	x	x			x				
	Neutrophil Count					x				
	C-reactive protein			x		x			x	x
	Albumin					x			x	x
	Vitamin B12			x						
	Platelets					x				
	Urea					x				
	Alanine Transaminase					x				
	Alkaline Phosphatase					x				

*Performance status **Clinician Predicted Survival

Appendix 1

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update, Embase Classic+Embase <1947 to 2015 Week 14>
Search Strategy:
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1 neoplasm.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1024167)
2 cancer.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3421033)
3 malignancy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (251965)
4 tumo?r$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3908264)
5 carcinoma.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1530087)
6 1 or 2 or 3 or 4 or 5 (6273610)
7 model.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (3945411)
8 tool.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (657880)
9 7 or 8 (4498731)
10 prognosis.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1151044)
11 prediction.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (498913)
12 progno$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (1332771)
13 10 or 11 or 12 (1765582)
14 terminal care.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (48093)
15 palliat$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (173421)
16 hospice.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sh, tn, dm, mf, dv, kw] (26506)
17 14 or 15 or 16 (217896)
18 6 and 9 and 13 and 17 (1735)
19 limit 18 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained] (1626)
20 limit 19 to english language (1499)
21 limit 20 to humans (1370)
22 remove duplicates from 21 (1088)

Appendix 2 – Tables 4-10

Table 4: The PaP

Criterion for PaP		Score
Dyspnoea	Yes No	1 0
Anorexia	Yes No	1.5 0
KPS	≥30 10-20	0 2.5
CPS (weeks)	>12 11-12 7-10 5-6 3-4 1-2	0 2 2.5 4.5 6 8.5
Total WBC (x 109/L)	Normal ≤8.5 High 8.6-11 Very High >11	0 0.5 1.5
Lymphocyte Percentage	Normal 20-40% Low 12-19.9% Very low <12%	0 1 2.5
Risk Group	30 day survival	Total Score PaP
A B C	>70% 30-70% <30%	0-5.5 5.6-11 11.1-17.2

Table 5: The D-PaP

Criterion for D-PaP		Score
Dyspnoea	Yes No	1 0
Anorexia	Yes No	1.5 0
KPS	≥30 10-20	0 2.5
CPS (weeks)	>12 11-12 7-10 5-6 3-4 1-2	0 2 2.5 4.5 6 8.5
Total WBC (x 109/L)	Normal ≤8.5 High 8.6-11 Very High >11	0 0.5 1.5
Lymphocyte Percentage	Normal 20-40% Low 12-19.9% Very low <12%	0 1 2.5
Delirium	Yes No	2 0
Risk Group	30 day survival	Total Score D-PaP
A B C	>70% 30-70% <30%	0-7 7.1-12.5 12.6-19.5

Table 6: The BCI

Total BCI score = multiply serum vitamin B12 level (pmol/l) by serum CRP level (mg/l)	
Risk Group	BCI Score
1 2 3	≤ 10000 10001-40000 >40000

Table 7: The PiPS (A and B)

PiPS A	PiPS B	Score
Breast cancer Male Genital Organs Distant metastases Liver metastases Bone metastases Mental test score (0-10) Pulse (bpm) Anorexia Dyspnoea Dysphagia Loss of weight in previous month ECOG (0-4) Global Health (1-7)	Male Genital Organs Distant metastases Bone metastases Mental test score (0-10) Pulse (bpm) Anorexia Fatigue ECOG (0-4) Global Health (1-7) WBC Neutrophils Lymphocytes Platelets Urea ALT Alk Phos Albumin CRP	The presence/absence of the indices is entered into electronic tool which calculates survival

Table 8: The PPI

Criterion		Score
Palliative Performance Scale	10-20 30-50 ≥60	4 2.5 0
Oral Intake	Severely reduced Moderately reduced normal	2.5 1 0
Oedema	Present absent	1 0
Dyspnoea at rest	Present absent	3.5 0
Delirium	Present absent	4 0
Risk Group	Survival	PPI score
A B C	Longer than 6 weeks Shorter than 6 weeks Shorter than 3 weeks	≤4 >4 >6

Table 9: The PPS

PPS	Range	Level of Function/condition
	100% → 0%	Normal → Death

Table 10: The GPS/mGPS

	CRP	Alb	Score
GPS	CRP ≥ 10 mg/L CRP > 10 mg/L Normal CRP CRP > 10 mg/L	Albumin ≥ 35 g/L Normal albumin Albumin < 35 g/L Albumin < 35 g/L	0 1 1 2
mGPS	CRP ≤ 10 mg/L CRP > 10 mg/L CRP > 10 mg/L	albumin ≥ 35 g/L Normal albumin Albumin < 35 g/L	0 1 2

Appendix 3

PaP (Palliative Prognostic Score)and D-PaP (Delirium PaP) (Tables 4 and 5)

The PaP score was constructed by the Italian Multicentre and Study Group in Palliative Care and validated in patients with advanced incurable cancer using thirty day survival probability. The D-PaP (Delirium-PaP) is a modified version of the PaP, incorporating a delirium assessment which slightly improved the predictive accuracy of the PaP. The PaP and D-PaP are the only prognostic tools included in this review which use clinician predicted survival (CPS) as one of their indices. The PaP has six parameters; four subjective (clinical) and two objective (biomarkers). The PaP and D-PaP both rely heavily on Clinician Predicted Survival, a subjective parameter which can add an extra 8.5 points to the total score (PaP maximum 17.5; D-PaP maximum 19.5). The other parameters (biomarkers and symptoms) contribute a a maximum of 2.5 points making this tool heavily reliant on the clinician's expertise in prognostication.

A key component of the PaP is clinician predicted survival (CPS). It has been argued that CPS is dependent on physicians having sufficient knowledge and experience to make assess this adequately. From the eligible studies it was noted that oncologists' (i.e. non palliative care specialists) CPS was shown to be well calibrated but individual predictions imprecise. Using the CPS from non-specialists still enabled the PaP to predict the short term survival (30 days) of patients with advanced cancer 'reasonably well'. The inclusion of CPS, therefore, does not detract from the PaP score being a unique combination of physician's judgement, corrected and integrated with a series of other objective parameters, optimising the score. In spite of this, this tool is not used routinely. This may be due to its heavy reliance on CPS and therefore clinicians do not need to use a tool which weights their existing opinion heavily, and therefore they could argue will not alter their survival estimate. The other components of the tool have been individually validated for their accuracy in estimating prognosis, however the individual weighting of each parameter is not known since no study has compared every clinical and biomarker important in prognosis in advanced cancer.

BCI (B12/CRP Index) (Table6)

The BCI was developed by a group at the University of London, UK, following the EAPC's recommendations in 2005. It was initially validated in patients with advanced incurable cancer admitted to an elderly care facility. It can estimate up to 90 day mortality. Of interest

is that the BCI incorporates vitamin B12 levels as a marker of prognosis; the rationale for this is that increased levels are present in myeloproliferative disorders, hepatocellular carcinoma and metastatic liver disease. It consists of two objective (biomarker) parameters, CRP and B12. However, vitamin B12 is not always analysed routinely in patients and may explain the lack of further research into this tool.

PiPS (Prognosis in Palliative Care Study) (Table 7)

The PiPS was developed in a UK population with locally advanced or metastatic cancer. There are two versions of the tool (PiPS A and PiPS B) and differ in that PiPS B incorporates biomarkers when assessing survival. It predicts survival up to and greater than 55 days. The PiPS A has 13 subjective parameters whereas the PiPS B has nine subjective and eight objective (biomarker) parameters. The PiPS, similar to other tools, relies on subjective parameters however in this case, they are orientated towards specific symptoms, signs and disease burden and many are suggested by the EAPC as individual prognostic factors. The relative weighting of each of the prognostic factors is not available in the public domain, instead the tool is accessed electronically and a score issued.

PPI (Palliative Prognostic Index) (Table 8)

The PPI was developed in Japan in 1999, in patients with advanced incurable cancer. It divides survival into three groups and estimates survival up to 6 weeks. Risk group A (PPI score ≤4) has an estimated survival of more than six weeks. Risk group B (PPI score 5) has an estimated survival of less than six weeks but greater than three weeks. Risk group C (PPI score >6) has an estimated survival of less than three weeks. It consists of nine subjective parameters (the Palliative Performance Scale, oral intake, oedema, dyspnoea at rest and delirium) and reports the presence or absence of signs and symptoms with similar weighting given to the different parameters. One of the parameters used is the Palliative Performance Scale (PPS) that is a prognostic tool in its own right. By incorporating the PPS into the PPI, more subjective parameters are incorporated and whilst this may increase the prognostic accuracy, it may increases bias and the complexity and reduce clinical utility.

PPS (Palliative Performance Scale) (Table 9)

The PPS was validated in a palliative care population in Canada. It provides a percentage score based upon subjective indices giving a survival estimate up to 3 months. Survival

accuracy of intermediate scores has been noted to be variable. It consists of six subjective parameters. Many of these parameters are focussed on aspects of performance status including ambulation, activity levels and performance status itself. Performance status is the gold standard in assessing a patient's fitness, therefore this tool is bias towards performance status in that synonyms of performance status are included as parameters (e.g. levels of ambulation, activity and self-care). One of the other parameters is conscious level, which could have been objectified by incorporating the Glasgow Coma Scale.

In conclusion the PPS has been extensively studied in a large patient population with advanced cancer, including multiple cancer types. It has performed well in the majority of the studies looking at the tool individually, the only criticism being its better accuracy with lower PPS scores. It has also been compared several times with other prognostic tools with varying results and again demonstrates comparable accuracy to other tools with lower PPS scores. The components of this tool are heavily bias towards performance status and disease burden emphasising the importance of these clinical markers in prognosis.

GPS (the Glasgow Prognostic Score) (Table 10)

The GPS was originally developed in patients with non-small cell lung cancer and subsequently refined to the mGPS The GPS combines CRP and albumin to give a score of 0, 1 or 2, with increasing score suggesting decreased survival: CRP<10=0; CRP≥10=1 (albumin ≥35); and CRP>10 + Albumin<35 =2 It has been validated in individual cancer types in addition to large populations of patients with advanced incurable cancer. [23] The GPS is entirely objective as the information needed to calculate the score is based on biomarker results. The GPS has been developed since the EAPC's recommendations in 2005 and meets the requirements set that any prognostic tool is quick and easy to use, and its scoring system is very simple. The GPS is also able to predict survival accurately several months prior to death. It fulfils the EAPC's recommendations of being quick and easy to use, along with robust evidence of its accuracy.